REMARKS

Claims 1-6, 8-17 and 19-40 are pending; claims 19-36 have been withdrawn from examination as being drawn to nonelected subject matter. Claims 1-6, 8-17 and 37-40 were rejected under 35 U.S.C. §112, first paragraph. Claims 37-40 were rejected under 35 U.S.C. §112, second paragraph.

Claims 1, 8, 9, 11, 37, 38 and 39 have been amended herein without prejudice or disclaimer of any previously claimed subject matter.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Supplemental Information Disclosure Statement

Applicants request that the Examiner sign off on the Form PTO-1449 submitted on November 12, 2001.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-6, 8-17 and 37-40 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner asserts that "the effect of dopamine **replenishment** in specific areas of the brain is not known" and that "the specification does not adequately teach how to use the claimed method to produce the intended effect." Office Action, page 4, original emphasis. Applicants respectfully disagree with these assertions and submit that the specification provides adequate guidance to enable one skilled in the art to use the method as claimed.

Negative symptoms of schizophrenia are known to be associated with a hypodopaminergic state in the prefrontal cortex of the brain. In addition to Seibyl et al.[1], Davis et al. (1991, *Am. J. Psychiatry* 148:1474-1486; submitted November 12, 2001) state that "the negative/deficit symptom complex of schizophrenia may be associated with low dopamine activity in the prefrontal cortex."[2] Davis et al. report that blood flow in the prefrontal cortex of schizophrenic patients was increased after administration of dopamine agonists and suggests "that the hypofrontality found in schizophrenic patients can be redressed by increasing dopamine activity in the prefrontal cortex" (page 1480, column 2). Also see, for example, pages 1479-1480.

The claimed invention is directed to a method for providing dopamine or a dopamine precursor to a subject with schizophrenia through administering cells to the prefrontal cortex of the subject's brain. The cells, which produce dopamine or a dopamine precursor, are administered adhered to a support matrix and in an amount effective to alleviate a negative

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[1] Seibyl et al., U. S. Patent No. 5,447,948, was discussed in the response to the previous Office Action submitted November 5, 2001.

[2] See Davis et al. (1991), abstract.

symptom of schizophrenia. The method of the invention provides dopamine to an area of the brain of a schizophrenic patient in which low dopamine activity is associated with negative symptoms.

The specification teaches types of cells and types of support matrices appropriate for use in the claimed method. See, for example, pages 12-21. The specification teaches how to make the claimed cell support complex. See, for example, page 21, line 15, to page 22, line 6. The specification teaches administration of the claimed cell/support complex to the prefrontal cortex of a patient with schizophrenia. The specification provides guidelines as to site and means of administration of the complex and guidance as to the number of cells which produce dopamine or a dopamine precursor to be administered to the patient. See, for example, page 12, lines 1-6, and page 22, line 19, to page 23, line 11. The specification describes examples of negative symptoms of schizophrenia and standard methodology by which the symptoms may be assessed so that alleviation of a negative symptom can be determined. See, for example, page 7, line 21, to page 8, line 4, and page 23, lines 22-31.

Thus, Applicants submit that the specification provides all the required information for one of skill in the art to make and use the invention.

The Examiner repeated the assertion from the previous Office Action dated May 7, 2001 that the effects of ex vivo gene therapy and cell-based therapies are unpredictable. Applicants respectfully refer to page 6 of the response to the previous Office Action, submitted November 5, 2001, in which evidence was presented of administration of cells as described in the present invention has been successful in the amelioration of a deficit dopaminergic state at particular locations in the brain.

The Examiner states that the "specification discloses a wide variety of cell types that could be used, but does not offer a starting point with regards to a combination of therapeutic cells, protective cells and support cells that would be effective in treating the negative symptoms of schizophrenia." Office Action, page 5. Applicants respectfully disagree.

According to the invention, a "therapeutic cell" is defined as a cell which produces dopamine or a dopamine precursor. The specification describes types of cells that would be useful, as well as qualities that would make a cell useful, as a "therapeutic cell" for the invention. See for example, pages 12-17. In addition, the specification describes a "protective cell" of the invention as a cell which produces an immunologically privileged site and describes cell types and qualities of protective cells useful for the invention. See, for example, page 9, lines 14-25. The specification also describes a "support cell" of the invention as a cell which produces factors that improve the viability of the therapeutic cells and describes cell types and qualities of support cells useful for the invention. See, for example, page 9, line 26, to page 10, line 2.

Thus, the specification provides guidance and direction to one skilled in the art for the selection of therapeutic cells (i.e., cells that produce dopamine or a dopamine precursor) and, if desired, protective cells and support cells for administration in the claimed methods.

Applicants submit that the specification teaches how to make and use the claimed invention and that the pending claims are in compliance with the enablement requirements.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

Claims 37-40 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this ground for rejection.

Although Applicants believe that the claims were sufficiently definite when considered in view of the specification and the understanding of those of skill in the art, Applicants have attempted to respond to the concerns of the Examiner in order to enhance clarity and to facilitate disposition of the present case.

Applicants of course welcome any additional suggestions the Examiner may have and would appreciate the opportunity to discuss the claims with the Examiner after she has had an opportunity to review this Amendment and Response in order to ensure that the case can be placed into condition for allowance.

In view of the amendments, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' agent at the telephone number below.

If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the fee transmittal is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000600. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please amend claims 1, 8, 9, 11, 37, 38 and 39 as follows.

1. (Twice Amended) A method for providing dopamine or a dopamine precursor to a subject with schizophrenia, comprising administering a cell/support complex to the prefrontal cortex of the subject's brain, wherein said cell/support complex comprises [therapeutic] cells adhered to a support matrix, wherein said [therapeutic] cells produce dopamine or a dopamine precursor and wherein said cell/support complex is administered in an amount effective to alleviate a negative symptom of schizophrenia.

8. (Twice Amended) The method of claim 1, wherein the [therapeutic] cells are selected from the group consisting of retinal pigment epithelial cells, chromaffin cells, cells of neural origin, paraneural cells, cells engineered by somatic cell hybridization, cells derived from the adrenal medulla, and cells that have been genetically engineered to express dopamine or a dopamine precursor.

9. (Amended) The method of claim 8 wherein the [therapeutic] cells produce a dopamine precursor.

11. (Twice Amended) The method according to claim 8 wherein the [therapeutic] cells are retinal pigment epithelium (RPE) cells.

37. (Twice Amended) A pharmaceutical composition comprising therapeutic cells and Sertoli cells, wherein the <u>therapeutic cells and the Sertoli</u> cells are adhered to a support matrix.

38. (Twice Amended) A pharmaceutical composition comprising therapeutic cells, protective cells and support cells, wherein the therapeutic cells, protective cells and support cells are adhered to a support matrix.

39. (Twice Amended) A kit suitable for use in providing dopamine or a dopamine precursor to a subject with schizophrenia, comprising in a suitable packaging:

therapeutic cells that produce dopamine or a dopamine precursor;

protective cells;

support cells; and

a support matrix, wherein the therapeutic cells, protective cells and support cells can be adhered to the support matrix.